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REVIEW

Idiopathic Pulmonary Fibrosis for Cardiologists: Differential Diagnosis, Cardiovascular Comorbidities, and Patient Management

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ABSTRACT

The presence of rare comorbidities in patients with cardiovascular disease (CVD) presents a diagnostic challenge to cardiologists. In evaluating these patients, cardiologists are faced with a unique opportunity to shorten diagnosis times and direct patients towards correct treatment pathways. Idiopathic pulmonary fibrosis (IPF), a type of interstitial lung disease (ILD), is an example of a rare disease where patients frequently demonstrate comorbid CVD. Both CVD and IPF most commonly affect a similar patient demographic: men over the age of 60 years with a history of smoking. Moreover, IPF and heart failure (HF) share a number of symptoms. As a result, patients with IPF can be misdiagnosed with HF and vice versa. This article aims to increase awareness of IPF among cardiologists, providing an overview for cardiologists on the differential diagnosis of IPF from HF, and describing the signs and symptoms that would warrant referral to a pulmonologist with expertise in ILD. Once patients with IPF have received a diagnosis, cardiologists can have an important role in managing patients who are candidates for a lung transplant or those who develop pulmonary hypertension (PH). Group 3 PH is one of the most common cardiovascular complications diagnosed in patients with IPF, its prevalence varying between reports but most often cited as between 30% and 50%. This review summarizes the current knowledge on Group 3 PH in IPF, discusses data from clinical trials assessing treatments for Group 1 PH in patients with IPF, and highlights that treatment guidelines recommend against these therapies in IPF. Finally, this article provides the cardiologist with an overview on the use of the two approved treatments for IPF, the antifibrotics pirfenidone and nintedanib, in patients with IPF and CVD comorbidities. Conversely, the

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impact of treatments for CVD comorbidities on patients with IPF is also discussed.
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PLAIN LANGUAGE SUMMARY

Many patients with heart disease also have other medical conditions. This makes it harder for doctors specialized in treating heart disease (cardiologists) to treat these patients.

Idiopathic pulmonary fibrosis (IPF) is a rare lung disease. Patients with IPF often also have heart disease.

Many patients with IPF have to wait a long time to be diagnosed and sometimes they are given an incorrect diagnosis, for example, heart disease. This is because IPF and some types of heart disease have similar symptoms and both diseases most commonly affect men aged over 60 years who smoke or used to smoke. Raising awareness of IPF among cardiologists could help to reduce the number of patients with IPF receiving an incorrect diagnosis and could reduce the time it takes to receive a diagnosis.

Some patients have both IPF and heart disease. This is important because different heart diseases can affect the choice of medicines to prescribe for IPF. For example, many patients with heart disease also have kidney problems and other patients might have bleeding problems. Both of these factors might influence medication choice.

This article aims to raise awareness of IPF among cardiologists. It describes the signs and symptoms of IPF, and provides instructions to help cardiologists decide if a patient might have IPF. This article also provides information to help cardiologists decide what medicines to prescribe to patients who have both IPF and heart disease, and highlights the importance of doctors working together when they are treating the same patient.

INTRODUCTION

The presence of rare comorbid diseases in patients with cardiovascular disease (CVD) can present a diagnostic challenge to cardiologists. Idiopathic pulmonary fibrosis (IPF) is a type of interstitial lung disease (ILD; Fig. 1) and is an example of a rare disease where patients frequently demonstrate comorbid CVD [1–6]. Like CVD, IPF affects more men than women and is more frequent in current or ex-smokers, and the majority of diagnoses occur in patients over the age of 60 years [7–11]. In addition, IPF presents with a number of non-specific symptoms, for example, dyspnea, cough, and reduced exercise capacity, many of which can be mistaken for symptoms of heart failure (HF) [12, 13]. Pulmonologists are the specialists responsible for the definitive diagnosis and treatment of IPF. However, cardiologists may be in a privileged position to identify patients with a potential diagnosis of IPF earlier and refer them to pulmonologists, and thereby reduce the number of misdiagnoses, shorten diagnosis times, and direct patients towards correct treatment pathways [12, 14–16].

IPF is a debilitating, irreversible, and fatal ILD characterized by the formation of scar tissue and architectural distortion in the lungs, with a progressive decline in lung function and a median survival following diagnosis of between 2 and 5 years [6, 11, 17]. The cause of IPF is unknown and its clinical course is variable, with no way to accurately predict prognosis [1, 17]. The incidence of IPF in Europe and North America has been estimated to be between 3 and 9 cases per 100,000 of the population per year, and evidence suggests that the prevalence is increasing over time [18–20]. Currently, there are no treatments capable of reversing fibrotic lung damage in patients with IPF. However, there are two approved treatments for patients with IPF, the antifibrotics pirfenidone and nintedanib [21–24]. Both have been shown to significantly reduce lung function decline versus placebo over 52 weeks [25, 26]. In selected patients, lung transplantation (LTx) can help to prolong survival and improve functional status [11, 27, 28]. The early and correct diagnosis of

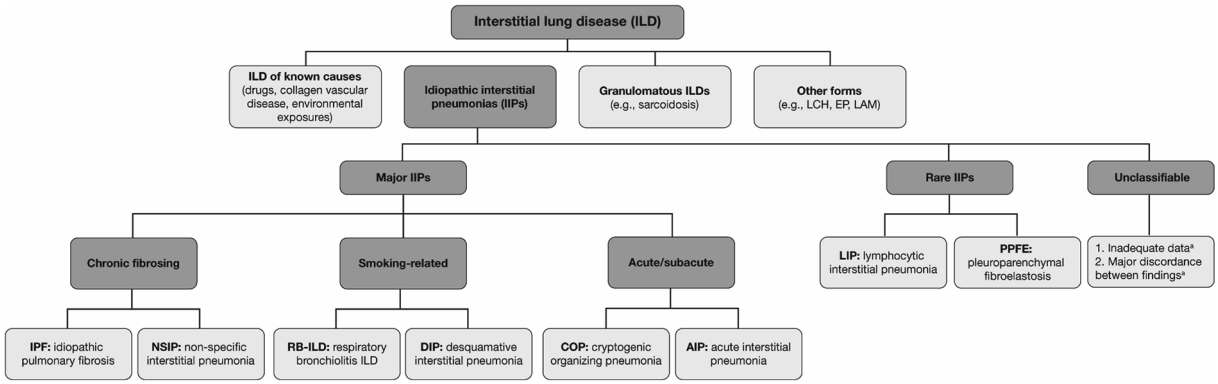

Fig. 1 Classification of ILDs [121–123]. *EP* eosinophilic pneumonia, *LAM* lymphangioleiomyomatosis, *LCH* Langerhans cell histiocytosis. [a]Clinical, radiological, pathological. This figure is based on previously published information. Permission for re-use has been granted for: Ryerson and Collard [122], https://journals.lww.com/co-pulmonarymedicine/Abstract/2013/09000/Update_on_the_diagnosis_and_classification_of_ILD.8.aspx. Reprinted with permission of the American Thoracic Society. Copyright © [2018] American Thoracic Society [121, 123].

IPF is instrumental to patients accessing treatments with the potential to slow disease progression and prolong survival.

Increased awareness of IPF is required across a range of clinical specialties to help the identification, diagnosis, and treatment [29]. This review aims to raise awareness of IPF among cardiologists by exploring a number of topics that are relevant to the cardiology community, including: differential diagnosis between IPF and HF; the prevalence of cardiovascular complications in patients with IPF, with a focus on pulmonary hypertension (PH); and the management of patients with comorbid IPF and CVD. This article does not contain any studies with human participants or animals performed by any of the authors.

DIAGNOSIS OF IPF

Diagnostic Delays in Patients with IPF

The diagnosis of IPF is often a protracted and challenging process, with many patients enduring extended delays before receiving a diagnosis [14, 30–32]. For example, some patients with IPF may be symptomatic up to 5 years before diagnosis, exhibiting breathlessness and/or cough [15]. In a review of referral letters of patients with IPF identified from the Finnish IPF registry, the mean (range) time between symptom onset and referral to a pulmonologist was 1.5 (0.8–2.3) years [32]. Similarly, in a prospective cohort study including 129 patients with IPF in the US, the median (interquartile range) reported delay between symptom onset and evaluation at a tertiary center was 2.2 (1.0–3.8) years [31]. The 2018 international (ATS/ERS/JRS/ALAT) guidelines describe the complexities of the diagnosis of IPF that, by its nature, is one of exclusion (Fig. 2) [1].

In particular, diagnostic delays may be introduced if patients are misdiagnosed or prescribed multiple treatments for other conditions before they are finally referred to an ILD specialist. For example, in two surveys of patients with pulmonary fibrosis, over 50% of patients reported an initial misdiagnosis. Although other respiratory conditions, such as bronchitis and asthma, were more likely to be misdiagnosed, heart disease was also a misdiagnosis in some patients [14, 16]. Delays in diagnosis have been associated with negative outcomes in patients with IPF, with longer delays associated with an increased risk of death independent of lung function [31]. Similarly, real-world results from the European EMPIRE registry have demonstrated a reduced median survival in

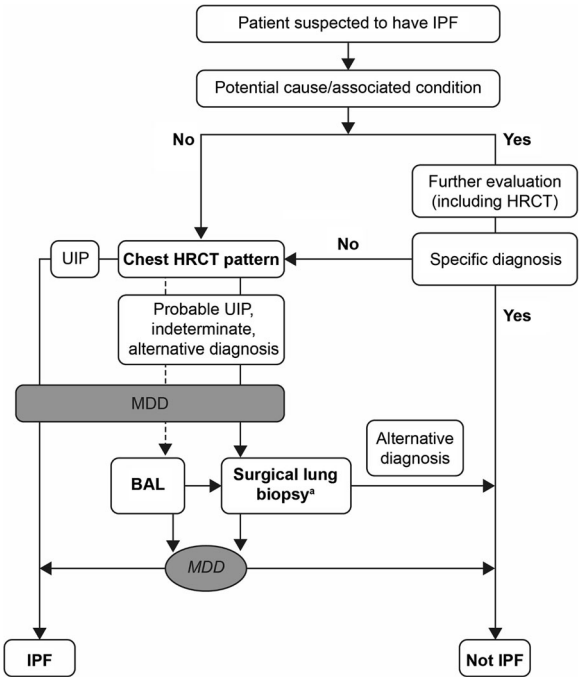

Fig. 2 Diagnostic algorithm for IPF from 2018 ATS/ERS/JRS/ALAT guidelines [1]. *ALAT* Latin American Thoracic Society, *ATS* American Thoracic Society, *BAL* bronchoalveolar lavage, *ERS* European Respiratory Society, *HRCT* high-resolution computed tomography, *IPF* idiopathic pulmonary fibrosis, *JRS* Japanese Respiratory Society, *MDD* multidisciplinary discussion, *UIP* usual interstitial pneumonia. [a]Surgical lung biopsy is not indicated in patients at high risk for intra-, peri-, or post-operative complications. Reprinted with permission of the American Thoracic Society. Copyright © [2018] American Thoracic Society [1]. The *American Journal of Respiratory and Critical Care Medicine* is an official journal of the American Thoracic Society

patients who waited over 12 months for a diagnosis of IPF versus those who waited less than 12 months [33].

Differential Diagnosis of IPF and HF

IPF presents with non-specific symptoms such as dyspnea, which can be present in a variety of other conditions, including HF, asthma, chronic obstructive pulmonary disease, pulmonary thromboembolism, or pneumonia [11, 12]. In particular, IPF and HF can be particularly challenging to distinguish from each other [34], as both conditions commonly present with dyspnea and reduced exercise tolerance (Table 1) [6, 12, 35]. Furthermore, there is considerable overlap between the populations most affected by IPF and CVD, with both conditions being more common in men over the age of 60 years with a history of smoking [7–11].

Table 1 Signs and symptoms of IPF and heart failure

Similarities between IPF and heart failure
Dyspnea
Reduced exercise tolerance
Fatigue
Cough
Weight loss[a]
Reduced FVC and other lung volumes
Differences between IPF and heart failure
IPF
Finger clubbing
Velcro® crackles
No pleural effusions
Heart failure
Unexplained weight gain
Peripheral edema
Orthopnea
Coarse crackles
Possible pleural effusions

FVC forced vital capacity, *IPF* idiopathic pulmonary fibrosis

[a] Cardiac cachexia can lead to weight loss

A detailed medical history and physical examination can provide a number of useful observations, which may help to guide further investigations and distinguish IPF from HF (Table 2). Dyspnea accompanied by bilateral edema, orthopnea, increased jugular venous pressure, a displaced apical beat, and bilateral posterior inspiratory crepitations/smooth

Table 2 Diagnostic findings in IPF and heart failure

BNP/NT-proBNP	A diagnosis of heart failure can be considered in patients with BNP > 35 pg/ml or NT-proBNP > 125 pg/ml; however, elevated levels do not necessarily rule out IPF
Pulmonary function	Patients with IPF typically demonstrate impaired lung function on spirometry[a]; however, some patients with acute decompensated heart failure can also show impairment
6MWD	Reduced exercise tolerance can be present in IPF and heart failure
Chest radiograph	Patients with IPF sometimes show decreased lung volumes and subpleural reticular opacities that increase from the apex to the base of the lung; however, a normal chest radiograph does not rule out IPF
HRCT	Patients with IPF demonstrate a usual interstitial pneumonia pattern on HRCT images of the chest
Arterial blood gases	Patients with IPF typically demonstrate hypoxemia
ECG	Patients with heart failure typically show ECG abnormalities
Echocardiography	Patients with IPF may show pulmonary hypertension. Patients with heart failure typically show structural or functional cardiac abnormalities on echocardiography

6MWD 6 min walk distance, *BNP* brain natriuretic peptide, *DLco* carbon monoxide diffusing capacity, *ECG* electrocardiography, *FEV_1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *HRCT* high-resolution computed tomography, *IPF* idiopathic pulmonary fibrosis, *NT-proBNP* N-terminal prohormone BNP

[a] Reduced FVC and increased FEV_1/FVC ratio on spirometry, along with reduced DLco

crackles at the lung bases in a patient with a history of coronary artery disease (CAD), arterial hypertension, or diuretic use would obviously warrant further investigation of a diagnosis of HF [12, 35]. However, dyspnea accompanied by fine 'Velcro®' crackles on auscultation at the posterior lung bases, or evidence of clubbed fingers, which are present in 25–50% of patients with IPF, would instead indicate that the patient should be referred to an ILD specialist for further investigation [7, 12, 13]. Velcro® crackles, considered characteristic of IPF, have been compared with the sound of gently separating Velcro®, and are thought to be the first abnormality on physical examination of patients with IPF [36]. Velcro® crackles in IPF are bibasal, mostly present for the entire inspiratory time (pan-inspiratory), fine in quality, and persist after deep breaths and coughing. As IPF progresses they may be auscultated higher in the bases and heard throughout the lower lobes [36]. Although Velcro® crackles are not specific for IPF, their presence accompanied by dyspnea, gas-exchange abnormalities, and lung infiltrates should prompt referral to an ILD specialist [36]. Similarly, referral should be considered if crackles are not accompanied by ancillary features associated with HF (for example, peripheral edema, elevated central venous pressure) or bilateral pneumonia (for example, fever, colored phlegm).

In patients in whom a detailed medical history and physical examination does not lead to an obvious diagnosis, there are a number of additional tests that can exclude or confirm diagnoses of IPF or HF (Table 2). Plasma levels of natriuretic peptides, such as brain natriuretic peptide (BNP) or N-terminal prohormone BNP (NT-proBNP), are extremely useful for the diagnosis of HF [12, 35, 37]. HF can typically be excluded in patients with normal levels of BNP or NT-proBNP (BNP ≤ 35 pg/ml and/or NT-proBNP ≤ 125 pg/ml) [35]; however, it should be noted that elevated levels do not necessarily rule out a diagnosis of IPF [38, 39]. When elevated levels of BNP or NT-proBNP are confirmed, echocardiography is mandatory to confirm structural or functional cardiac abnormalities [35].

Table 3 Diagnostic categories of UIP based on CT patterns. Reprinted from Lynch et al. [44], with permission from Elsevier

	Typical UIP CT pattern	Probable UIP CT pattern	CT pattern indeterminate for UIP	CT features most consistent with non-IPF diagnosis
Distribution	Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous	Basal and subpleural predominant; distribution is often heterogeneous	Variable or diffuse	Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing
Features	Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis[a]; absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis[a]; honeycombing is absent; absence of features to suggest an alternative diagnosis	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern	Any of the following: predominant consolidation, extensive pure ground-glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts

CT computed tomography, *IPF* idiopathic pulmonary fibrosis, *UIP* usual interstitial pneumonia

[a] Reticular pattern is superimposed on ground-glass opacity, and in these cases it is usually fibrotic. Pure ground-glass opacity, however, would be against the diagnosis of UIP or IPF, and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions

To investigate a potential diagnosis of IPF, lung function and oxygen saturation should be measured (Table 2) [11]. Patients with IPF typically demonstrate impaired lung function on spirometry, with reductions in forced vital capacity (FVC) and carbon monoxide diffusing capacity (DLco) being the most common findings [11, 40, 41], although some patients with HF may also show lung function abnormalities. Mild left HF is a recognized cause of increased DLco, due to increased pulmonary capillary blood flow; more significant HF is associated with restriction on pulmonary function tests and a low DLco, and patients may have mild obstruction on spirometry arising from small airway edema [41, 42]. Hypoxemia is highly suggestive of IPF as it is extremely rare in patients with isolated HF, and can be detected through the measurement of arterial blood gases [7]. In the cardiology outpatient setting, where measurement of arterial blood gases may not be feasible, pulse oximetry is usually a readily available method to identify gas-exchange abnormalities [7].

Ultimately, imaging of the chest is required to confirm a diagnosis of IPF (Table 2). If a chest X-ray is available, decreased lung volumes and subpleural reticular opacities that increase from the apex to the base of the lung are likely to be observed in patients with IPF [43]. However, a normal chest X-ray does not rule out IPF and, therefore, in the correct clinical setting, diagnosis of IPF should be confirmed with a high-resolution computed tomography (HRCT) image of the chest, with a pattern of typical or probable usual interstitial pattern (UIP) considered diagnostic (Table 3) [44]. UIP is defined as the presence of reticular opacities and clustered cystic airspaces, referred to as honeycombing, which are typically found in the basal and

peripheral regions of the lungs [11]. However, it should be noted that the presence of a typical UIP pattern on HRCT is not specific for a diagnosis of IPF because it can also be present in other ILDs, for example, chronic hypersensitivity pneumonitis and connective tissue disease-associated ILD [45]. It is therefore imperative that a pulmonologist conducts a comprehensive clinical evaluation to identify any potential known causes of ILD. As confirming a diagnosis of IPF can be cumbersome, experts recommend the involvement of an ILD multidisciplinary team to establish an IPF diagnosis, typically involving a pulmonologist, a radiologist, and a pathologist (all experts in ILD within their specialty), among other members [1].

COMORBIDITIES AND COMPLICATIONS IN PATIENTS WITH IPF

Cardiovascular Comorbidities in Patients with IPF

It is important to note that, in many patients, CVD is diagnosed before IPF [46]. Comprehensive cardiovascular evaluation represents an opportunity for cardiologists to identify undiagnosed IPF in patients with CVD and refer them to a pulmonologist with expertise in ILD.

Patients with IPF demonstrate a high burden of CVD, with a number of studies reporting an increased risk of CVD in patients with IPF versus those without [3–5, 47]. Although respiratory failure is the most frequent cause of death in patients with IPF, CVD is still responsible for up to 10% of deaths [39, 48, 49]. The presence of cardiovascular comorbidities in patients with IPF and the effect on mortality have been investigated in several studies. For example, in a retrospective study of patients with pulmonary fibrosis treated at a single hospital in Finland, CVD remained associated with increased mortality in multivariate analyses adjusted for age, gender, smoking status, and percent predicted DLco [46]. Similarly, in a study including data from 272 patients with IPF from an ILD tertiary referral center, atherosclerosis and 'other' cardiac diseases were associated with increased mortality [50].

PH in Patients with IPF

PH is currently classified into five categories, which are differentiated by multiple factors including hemodynamic characteristics and pathological findings [51]. Group 3 PH is associated with lung disease and is a common cardiovascular complication diagnosed in patients with IPF, with prevalence varying between 3% and 86% but most often found to be between 30% and 50% [39, 52–57]. The presence of PH in patients with IPF is associated with a number of negative outcomes. For example, in a retrospective cohort study including data obtained from a US healthcare database on 6013 LTx candidates with IPF who were followed-up until death, LTx, or any other censoring event, 'mild' and 'severe' PH were significantly associated with mortality [58].

The pathophysiologic mechanisms accounting for PH in patients with IPF are complex [39]. Hypoxemic vasoconstriction and destruction of the pulmonary vascular bed by fibrosis, as well as aberrant angiogenesis and endothelial dysfunction, are likely to influence the development of PH [39, 59, 60]. However, the biological processes underlying progressive fibrogenesis may also be contributing factors as profibrogenic cytokines are also vasoactive [39, 59–62]. In addition, other common comorbidities in patients with IPF, such as emphysema, obstructive sleep apnea (OSA), thromboembolic disease, and HF are also likely to contribute to the development of PH [39]. In particular, the fibrotic lung tissue from patients with IPF is reported to increase levels of coagulation factors and their downstream activators [63, 64]. Venous thromboembolism has been used as a proxy for such a 'procoagulant state' and has been linked to interstitial idiopathic pneumonia (of which IPF is part; Fig. 1), especially amongst those never treated with anticoagulants [65].

The symptoms of PH are non-specific and overlap with those of IPF, including dyspnea, exercise intolerance, and fatigue [39, 66]. This

Table 4 Randomized placebo-controlled clinical trials investigating Group 1 PH treatments in patients with ILD and Group 3 PH

Study	Population (%PH)	Therapy	Primary outcome	Summary/result
ARTEMIS-PH [39, 117]	40 patients with comorbid IPF and PH (100%)	Ambrisentan	Change from baseline in 6MWD at week 16	Terminated early due to a lack of efficacy
ARTEMIS-IPF [118]	492 patients with IPF with (10%) and without comorbid PH	Ambrisentan	Time to IPF progression, defined as the first occurrence of death, respiratory-related hospitalization, or categorical decline in lung function[a]	Terminated early due to an interim analysis indicating a low likelihood of efficacy, with a potential increase in the risk of disease progression and respiratory-related hospitalization
RISE-IIP [69]	147 patients with comorbid idiopathic interstitial pneumonia and PH (100%)	Riociguat	Change from baseline in 6MWD at week 26	Terminated early due to an increased risk of death or serious adverse events in the active treatment arm
BPHIT [119]	60 patients with comorbid fibrotic interstitial pneumonia and PH (100%)	Bosentan	Percentage of patients with change from baseline in pulmonary vascular resistance index $\geq$ 20% over 16 weeks	Completed. No significant treatment effect versus placebo over 16 weeks on pulmonary hemodynamics, functional capacity, or symptoms
STEP-IPF [70]	180 patients with advanced IPF (percent predicted DLco $<$ 35%) with or without comorbid PH (% not reported)	Sildenafil	Percentage of patients with increase from baseline in 6MWD $\geq$ 20% at week 12	Completed. No significant treatment benefit versus placebo on the primary endpoint, although significant benefits were observed for arterial oxygenation, percent predicted DLco, dyspnea, and QoL

Table 4 continued

Study	Population (%PH)	Therapy	Primary outcome	Summary/result
STEP-IPF sub-study [120]	119 patients with advanced IPF (percent predicted DLco < 35%) with (19%) or without right-sided ventricular systolic dysfunction	Sildenafil	Multivariate linear regression was performed to investigate the relationship between right ventricular abnormalities, sildenafil, and changes in 6MWD and QoL over 12 weeks	Completed. In patients with right-sided ventricular systolic dysfunction, sildenafil was associated with significantly less decline in 6MWD and significant improvements in QoL versus placebo over 12 weeks
NCT02951429 [71]	Patients with IPF with more advanced disease at risk of Group 3 PH (planned sample size = 176)	Sildenafil + pirfenidone	Percentage of patients with disease progression, defined as ≥ 15% decline in 6MWD from baseline, respiratory-related non-elective hospitalization, or all-cause mortality over 52 weeks	Recruiting
NCT02802345 [72]	274 patients with IPF and percent predicted DLco ≤ 35%	Sildenafil + nintedanib	Change from baseline in SGRQ total score at week 12	Completed

6MWD 6 min walk distance, *DLco* carbon monoxide diffusing capacity, *FVC* forced vital capacity, *ILD* interstitial lung disease, *IPF* idiopathic pulmonary fibrosis, *PH* pulmonary hypertension, *QoL* quality of life, *SGRQ* St George's Respiratory Questionnaire

[a] Either ≥ 10% FVC decline and ≥ 5% DLco decline, or ≥ 15% DLco decline and ≥ 5% FVC decline

means that many patients with IPF are not evaluated for PH [39, 66]. The presence of PH should, however, be considered in every patient with IPF, especially when dyspnea or oxygen desaturation is disproportionate to the physiologic impairment demonstrated on pulmonary function testing or the findings on HRCT imaging [39, 53]. Other indicators of PH may include percent predicted DLco < 30%, unexpected reductions in 6 min walk distance (6MWD) often with oxygen desaturation to below 85%, and impaired heart-rate recovery after exertion [39, 53]. Although right-heart catheterization is considered the gold standard of diagnosis for Group 1 PH (pulmonary arterial hypertension), it is not systematically recommended in patients with IPF who exhibit the signs and symptoms of PH unless the patient is being considered for LTx, or if it is clinically indicated [56, 66]. When PH is suspected, quantification of NT-proBNP levels in patients with IPF can provide confirmation of whether further investigation is necessary [67]. A diagnosis of PH becomes very unlikely in patients

with NT-proBNP < 95 ng/l [67]. In patients with NT-proBNP ≥ 95 ng/l, a transthoracic echocardiogram can be used to look for signs of elevated right ventricular systolic pressure, such as dilation of the right atrium and/or ventricle, and right ventricular dysfunction [39]. The echocardiographic probability of PH can be defined as low, intermediate, or high based on a combination of peak tricuspid regurgitation velocity and the presence or absence of signs of PH on echocardiogram [56]. HRCT images of the chest may also assist with the identification of PH when showing a main pulmonary artery diameter > 29 mm or a pulmonary artery diameter greater than that of the aorta [66].

There are a number of therapies available for Group 1 PH, including calcium channel blockers, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs [56]. However, international treatment guidelines for IPF and PH do not recommend treating Group 3 PH in patients with IPF with the therapies available for Group 1 PH because of a lack of clinical evidence supporting the efficacy and safety of these treatments and the potential risk of impairing gas exchange through the inhibition of hypoxic vasoconstriction [56, 68]. Nevertheless, the guidelines do recommend that patients with IPF and PH and who are hypoxemic should receive long-term oxygen therapy [11, 56].

A number of randomized controlled trials have investigated therapies for Group 1 PH in patients with IPF and ILD with mixed and sometimes deleterious results (a comprehensive list is found in Table 4). For example, the RISE-IIP study of riociguat in patients with idiopathic interstitial pneumonia and PH was terminated early due to an increased risk of death or serious adverse events (AEs) in the active treatment group [39, 69]. The STEP-IPF trial of sildenafil in patients with advanced IPF, defined as percent predicted DLco < 35%, was completed but did not show a significant treatment benefit for the primary endpoint of the proportion of patients with an increase in 6MWD ≥ 20% at week 12 [70]. However, significant treatment benefits were observed for secondary endpoints versus placebo, including changes in arterial oxygenation, percent predicted DLco, dyspnea, and quality of life (QoL) after 12 weeks of treatment [70]. The use of sildenafil in combination with antifibrotics has recently attracted attention based on two randomized placebo-controlled clinical trials of patients with IPF [71, 72]. NCT02951429 is enrolling patients with IPF with more advanced disease (percent predicted DLco ≤ 40%) at risk of Group 3 PH, and will investigate the efficacy, safety, and tolerability of sildenafil added to pirfenidone over 52 weeks [71, 73]. The primary outcome is the percentage of patients with disease progression, defined as the occurrence of ≥ 15% decline in 6MWD, respiratory-related non-elective hospitalization, or all-cause mortality. Another trial, INSTAGE (NCT02802345), enrolled patients with IPF and advanced lung-function impairment (percent predicted DLco ≤ 35%), and investigated the efficacy and safety of sildenafil added to nintedanib over 24 weeks [72]. The primary outcome was the change from baseline at week 12 in St George's Respiratory Questionnaire (SGRQ) total score. These results were recently reported and showed that the difference in change from baseline in the SGRQ total score between the nintedanib and sildenafil treatment arm and the nintedanib alone arm was not significant at weeks 12 or 24 [74]. A large number of exploratory outcomes showed no benefit of adding sildenafil to treatment with nintedanib, with the exception that patients treated with nintedanib plus sildenafil had a lower risk of reaching a composite endpoint of absolute decline in percent predicted FVC of ≥ 5% or death than those treated with nintedanib alone [74]. The absence of an increase in BNP level in the patients who received nintedanib plus sildenafil in the trial may indicate a reduction in right ventricular stress [74].

Other Comorbidities in Patients with IPF

In addition to CVD and PH, other comorbidities, such as gastroesophageal reflux disease (GERD) and OSA, are frequently associated with IPF [75]. The precise prevalence of GERD amongst patients with IPF is difficult to ascertain because of differences in diagnostic procedures, but it may affect over 80% of individuals

[76, 77]. It has been hypothesized that GERD may contribute to the progression of IPF in some patients and studies exploring the effect of anti-acid therapy have been performed. In an analysis of the placebo arms of three IPF Clinical Research Network randomized clinical trials, those patients taking anti-acid medication at baseline had a slower decline in percent predicted FVC over 30 weeks [78]. A post hoc analysis of a separate clinical trial data set did not replicate this result and a more recent Phase II clinical trial of omeprazole in patients with IPF has yet to report (NCT02085018) [79, 80].

OSA is a frequent comorbid condition in patients with IPF, with a reported prevalence between 58% and 88% [53]. Despite this high reported prevalence, surprisingly few patients are evaluated for OSA [53]. If left untreated, OSA can result in nocturnal hypoxemia, the presence of which was recently shown to predict worsened survival in patients with IPF [81]. Moderate-to-severe OSA is generally treated with continuous positive airway pressure and this treatment has been shown to improve QoL measures in patients with IPF [53].

MANAGEMENT OF PATIENTS WITH IPF: CONSIDERATIONS FOR CARDIOLOGISTS

Antifibrotics

Two therapies are currently available for the treatment of patients with IPF, the antifibrotics pirfenidone and nintedanib [21–24]. Pirfenidone is an antifibrotic, anti-inflammatory, and anti-oxidant compound [82]. Its direct mechanism of action in IPF is not fully established [82]. Nintedanib is a tyrosine kinase inhibitor, which mainly inhibits receptors for platelet-derived growth factor, fibroblast growth factor, and vascular endothelial growth factor (VEGF) [83]. Neither treatment can reverse the fibrotic damage associated with IPF. However, both pirfenidone and nintedanib have been shown to reduce lung-function decline versus placebo in pivotal Phase III clinical trials [25, 26]. A pooled analysis of the pirfenidone pivotal Phase III trials, ASCEND and CAPACITY, demonstrated that, at 1 year and compared with placebo, pirfenidone reduced the proportion of patients with a decline in percent predicted FVC or death by 44% [26]. In the nintedanib pivotal Phase III trials, nintedanib reduced the annual rate of change in FVC versus placebo by 125 ml in INPULSIS-1 and by 94 ml in INPULSIS-2 [25].

Considering survival, the pirfenidone pivotal Phase III trials were not individually powered to show a difference, but a pooled analysis and meta-analyses concluded that pirfenidone significantly reduced mortality versus placebo over 120 weeks [84]. A meta-analysis of the nintedanib Phase II TOMORROW and Phase III INPULSIS trials found trends for reduced mortality versus placebo over 52 weeks [85]. It remains unknown to what extent increased use of antifibrotics may influence long-term survival in IPF.

The safety and tolerability of pirfenidone and nintedanib have been extensively characterized, and the most common AEs with both drugs are gastrointestinal, with the potential for rashes with pirfenidone [85, 86]. No clinical trial has, as yet, specifically explored the use of antifibrotics in patients with IPF and cardiovascular comorbidity. However, the cardiovascular safety and tolerability profiles of pirfenidone and nintedanib are evidenced by findings from the pivotal Phase III trials.

There is a minor concern that the effect of nintedanib on VEGF may lead to a small increased risk of non-serious bleeding events and the US and European product labels specify that patients at known risk for bleeding should only receive nintedanib if the anticipated benefit outweighs the risk [21, 24, 87]. Cardiologists may wish to consider the potential for bleeding events in their patients who are taking nintedanib for IPF and who require anticoagulation or antiplatelet therapy for comorbid conditions [21]. In the Phase III pivotal INPULSIS trials of nintedanib, where patients at known risk for bleeding were excluded, serious bleeding events had a low incidence and occurred at a similar frequency in both treatment arms (nintedanib 1.3% and placebo 1.4%) [21]. Of note, the most frequent bleeding event was non-serious epistaxis, a finding that is supported by post-

marketing surveillance data [88]. Caution is urged when prescribing nintedanib in patients with IPF and a history of abdominal surgery, peptic ulceration, or diverticular disease, and patients who are prescribed corticosteroids or non-steroidal anti-inflammatory medications [21]. Regular monitoring of blood pressure in patients treated with nintedanib is also recommended in Europe, presumably because nintedanib inhibits the VEGF pathway and oncology studies have shown that anti-VEGF therapy frequently leads to hypertension in patients with renal cancer [21, 89, 90]. When prescribing pirfenidone in patients with IPF, there are no special warnings or precautions surrounding bleeding events that require consideration [22]. In a retrospective blinded review of data from the pivotal Phase III ASCEND and CAPACITY clinical trials, presented as a conference abstract (not yet subjected to peer review in the form of an original research article), the pooled incidence of bleeding events was 3.7% and 4.3% in the pirfenidone and placebo treatment arms, respectively [91].

The more general cardiovascular safety and tolerability of pirfenidone and nintedanib were also assessed in the Phase III clinical trials. In the same retrospective blinded review of data from ASCEND and CAPACITY, again presented as a conference abstract (not yet subjected to peer review in the form of an original research article), the pooled incidence of major adverse cardiovascular events (cardiac arrest, myocardial infarction, stroke, and unstable angina) was 1.4% and 2.1% in the pirfenidone and placebo arms, respectively [92]. In the INPULSIS trials, cardiac AEs were reported by 10.0% and 10.6% of patients treated with nintedanib and placebo, respectively, and serious cardiac AEs were reported by 5.0% and 5.4% of patients, respectively [25]. Real-world evidence for both pirfenidone and nintedanib has suggested that the safety and tolerability of these drugs in clinical practice is similar to the Phase III trials [93–99]. Furthermore, the ongoing clinical trials should provide more extensive information on the effect of these antifibrotic drugs in combination with treatments for PH [100].

A further consideration for cardiologists and pulmonologists making prescribing decisions in patients with cormorbid IPF and heart disease is renal disease. Findings from clinical studies demonstrate that patients with heart failure frequently have renal impairment [101, 102]. The use of antifibrotics in patients with IPF and renal impairment has not been specifically studied, and the Phase III clinical trials present little or no information on renal AEs [25, 103, 104]. According to the US product label, pirfenidone should be used with caution in patients with any renal impairment, and its use is not recommended in patients with end-stage renal disease requiring dialysis [23]. According to the European product label, pirfenidone should be used with caution in patients with moderate renal impairment (creatinine clearance 30–50 ml/min) and should not be used in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease requiring dialysis [22]. Renal events are not listed as an adverse reaction of interest with pirfenidone in the product labels [22, 23]. With nintedanib, the European product label states that patients should be monitored during therapy, with particular attention to those patients exhibiting risk factors for renal impairment/failure [22]. In case of renal impairment/failure, therapy adjustment should be considered [22]. The pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment or end-stage renal disease requiring dialysis [24]. Physicians should also be aware that hepatic impairment is a further special consideration when managing patients with IPF on antifibrotics [21–24].

Other Medications for Patients with IPF

Corticosteroids should not be used in IPF, with the exception that they can be considered in patients experiencing an acute worsening of their condition (acute exacerbation) [11]. International guidelines for the treatment of IPF recommend against the use of long-term corticosteroid therapy [11]. Triple therapy with a combination of prednisone, azathioprine, and N-acetylcysteine was investigated in the PANTHER-IPF (NCT00650091) study in patients

with mild-to-moderate lung-function impairment [105]. An interim analysis revealed that there was an increased risk of death and hospitalization in patients receiving triple therapy compared with placebo. This resulted in early termination of the trial, and provided compelling evidence against the combined use of corticosteroids and immunosuppressants in patients with IPF [105].

Cardiovascular Medications in Patients with Comorbid IPF and CVD

When treating patients with comorbid IPF and CVD, it is important to take a holistic approach that keeps in mind the potential burden of polypharmacy in this population [39, 46, 50, 106]. A high proportion of patients with IPF are prescribed statins for cardiovascular indications [107]. In an analysis of data from 22,941 patients with ILD, including 5915 with IPF, in the national Danish Patients Registry, statins were associated with a reduced risk of mortality in patients with ILD and IPF [108]. Similarly, in a post hoc analysis of data from 624 patients randomized to placebo in the pivotal Phase III trials of pirfenidone, patients receiving statins at baseline had a significantly lower risk over 52 weeks for death or 6MWD decline, all-cause and respiratory-related hospitalization, and IPF-related mortality versus patients who were not receiving statins [107]. It should be noted that this post hoc analysis did not investigate outcomes in patients enrolled in the pirfenidone arms of the ASCEND and CAPACITY trials [107]. In a post hoc analysis of patients enrolled in the INPULSIS trials, there was a reduction in annual adjusted FVC decline in patients treated with statins compared with non-users, in both the nintedanib arm and the placebo arm [109]. The treatment effect of nintedanib versus placebo appeared to be consistent between patients who were treated with statins and those who were not [109]. Overall, in the absence of randomized controlled trials investigating statins in patients with IPF, the available evidence suggests that statins might have favorable effects on outcomes in IPF.

In addition to statins, anticoagulants are also commonly prescribed in patients with IPF for comorbid conditions such as atrial fibrillation and venous thromboembolic disease [110]. Theories regarding a potential link between thrombosis and lung fibrosis have previously led to suggestions that anticoagulants could have a role in the treatment of IPF [68]. However, treatment guidelines recommend against the use of anticoagulants for the treatment of IPF, based on concerns regarding the benefit–risk profile [68]. For example, the efficacy and safety of warfarin for treatment of IPF was investigated in the placebo-controlled ACE-IPF trial where 145 patients were randomized to receive warfarin or placebo. Due to a low probability of benefit and a significantly higher mortality rate in patients receiving warfarin versus placebo (14 deaths vs. 3 deaths; $p = 0.005$), the study was terminated early [111].

In a post hoc analysis of patients enrolled in the placebo arms of the ASCEND and CAPACITY trials, 32 patients who were treated with anticoagulants at baseline (91% of whom received warfarin) for conditions other than IPF were at a higher risk of IPF-related mortality over 52 weeks compared with non-users [112]. The risk of bleeding and cardiac events did not appear to differ between groups [112]. Based on the available evidence, individual risk assessments should be performed for each patient with IPF requiring anticoagulation, and post-marketing safety data on antifibrotics may prove useful at this point [88, 113]. There is obviously an unmet need for future clinical studies to investigate the use of anticoagulants other than warfarin in patients with IPF.

The relationship between the use of other cardiovascular medications and outcomes in patients with IPF has also been investigated in an analysis of data from 272 patients treated at a tertiary referral center for ILD [50]. Predicted survival was not significantly different in treated versus untreated patients for antiplatelet therapy, anticoagulants, beta blockers, statins, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and other antihypertensive drugs [50]. Further clinical research is required to investigate the effects of comorbidities and their treatments on

outcomes in IPF, including lung function, QoL, and survival.

Lung Transplantation

LTx has been shown to provide a survival benefit in patients with IPF, with a median post-transplant survival of 4.5 years [114]. International Guidelines for the Selection of Lung Transplant Candidates suggest that patients with IPF might be considered for LTx if they meet the following criteria: ≥ 10% FVC decline during a 6-month period, ≥ 15% DLco decline during a 6-month period, desaturation to < 88% or distance < 250 m during a 6 min walk test or > 50 m decline in 6MWD during a 6-month period, PH on right-heart catheterization or echocardiography, or hospitalization due to respiratory decline, pneumothorax, or acute exacerbation [28]. Potential candidates for LTx with IPF should be referred to a cardiologist as part of their pre-transplant workup. Guidelines for the selection of LTx candidates state that CAD not amenable to revascularization is an absolute contra-indication for LTx [28]. However, a registry study utilizing coronary angiography data from 644 patients who received LTx revealed that 324 patients had CAD, and that there was no difference in mortality between those with and without CAD [115]. Whilst the population of this study was screened, it does suggest that careful evaluation and treatment can allow for selected patients with CAD, including those requiring revascularization, to successfully undergo LTx.

CONCLUSION

In conclusion, both CVD and IPF share a number of risk factors and affect a similar patient demographic [53]. In addition, some of the signs and symptoms of HF are shared with IPF [14, 16]. In combination with the high prevalence of CVD in patients with IPF, these factors mean that cardiologists may be in a privileged position to identify patients with possible IPF and refer them to a specialist in ILD. The high burden of CVD in patients with IPF also means that cardiologists may have an important role in co-managing affected patients [10, 46]. This includes assessing patients for PH, one of the most frequent cardiovascular complications in patients with IPF [52, 54–56, 116].

Increased knowledge among cardiologists regarding the identification and diagnosis of patients with IPF will help to facilitate the diagnosis and treatment of these patients. In addition, increased knowledge among cardiologists regarding the management of patients with comorbid IPF and CVD will help to promote the holistic and multidisciplinary treatment of patients with both conditions.

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